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MARILYN L. AMICK
ROCHE DIAGNOSTICS CORPORATION
9115 HAGUE ROAD
P.O. BOX 50457
INDIANAPOLIS, IN 46250

EXAMINER
GARCIA, MAURIE E

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Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary	Application No. 08/776,190	Applicant(s) Josel et al
	Examiner Maurie E. Garcia, Ph. D.	Art Unit 1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 7, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *72-89 and 100-106* is/are pending in the applica

4a) Of the above, claim(s) *78, 79, 82, 89, and 102* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *72-77, 80, 81, 83-88, 100, 101, and 103-106* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 29

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Please note the change in examiner.

1. The Response filed November 7, 2001 via fax (Paper No. 28) is acknowledged. Claims 103-106 were added and no claims were amended or cancelled. Further consideration has necessitated new rejections. Since the new rejections were not necessitated by amendment to the claims, the case is maintained in non-final status.

2. Applicant's previously elected (Papers No. 19 & 22) species of amino acids as monomer units, hormones as haptens and luminescent metal chelates as marker groups are noted. There is currently no allowable generic claim, thus claims 78, 79, 82, 89 and 102 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to non-elected species. See paragraph 4 below, section highlighted in **bold**.

3. Moreover, to clarify the record, the following is noted: claim 85 is not drawn to the elected species and should have been withdrawn from consideration. However, since this claim has previously been examined, it will remain under examination in this Office Action.

4. Applicant's attention is directed to MPEP § 803.02 (emphasis added) regarding election of species:

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the

Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species***. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 72-77, 80, 81, 83-88, 100, 101 and 103-106 are examined in this action to the extent of the elected species.

Response to Arguments and Withdrawn Rejections

6. All of the previous rejections under 35 USC 112, 102 and 103 are withdrawn. However, please note that some of these rejections have been rewritten and are newly presented below. Applicant's arguments have been fully considered but are moot in view of the new ground(s) of rejection.

Specification

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). See page 26, lines 5 and 6 of the instant specification. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 72-77, 80, 81, 83-88, 100, 101 and 103-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claims are directed to conjugates that are defined in functional terms. The claims use generic terminology such as "hapten", "marker group", "solid phase binding group" "reactive side groups", "predetermined positions" and "non-immunologically reactive". These terms are set forth in the instant disclosure but the definitions are relative, broad and/or completely open-ended.

There are an unknown number of conjugates that would fall within the claimed genus for the following reasons. Claims 72, 74-77, 80, 83, 100, 101 and 103-106 contain no structural information whatsoever on the "haptens" and

"marker groups" or "solid phase binding groups". The entities in question could encompass widely varying structures. Also, it is unclear how "non-immunologically reactive" a carrier would have to be in order to be encompassed by this limitation (see further rejections under 35 USC 112, second paragraph below). Instant claims 73, 81 and 84-88 set forth some structural information on either the hapten or marker group but still do not fully define the structure of the claimed conjugates or specifically set forth a chemical structure for any of the entities that compose them.

The instant specification discloses *only* conjugates containing amino acid carriers with luminescent metal chelate marker groups and small organic molecule haptens that are attached through reactive amino side groups. Applicant's claimed scope represents only an invitation to experiment regarding other possible "haptens", "marker groups", "solid phase binding groups" and "reactive side groups". The claimed scope encompasses nucleotides as the "polymeric carrier" which are also not sufficiently described in the instant specification. Additionally, specifically with respect to claim 85, the recitation that the "polymeric carrier has a helical structure" is not supported by adequate description as there are no specific examples of such carriers and further how to attach the instant haptens and other groups thereto. Thus, the application fails to describe sufficient examples of conjugates that are within the scope of the presently claimed invention.

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Therefore it is deemed that the disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned. This further evidences that the structural features of the exemplified conjugates do not constitute support for the claimed genus or a substantial portion thereof.

10. Claims 72, 74-77, 80, 81, 83-88, 100, 101 and 106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugates where

the polymeric carrier comprises amino acids as the monomeric units, does not reasonably provide enablement for conjugates where the polymeric carrier comprises nucleotides as the monomeric units. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with *specific* polymeric carriers that comprise amino acids (or modified versions thereof); however, there is insufficient guidance as to how to make/use conjugates where the polymeric carrier comprises nucleotides as the monomeric units. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to conjugates that comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-10 "hapten molecules" and 1-10 "marker

groups or solid phase binding groups". These moieties are attached to the polymeric carrier via "reactive side groups" at "predetermined positions". Such represents very broad scope.

(3 and 5) The state of the prior art and the level of predictability in the art: Conjugates that comprise peptidic backbones that have certain specific "hapten molecules" and "marker groups or solid phase binding groups" attached thereto via "reactive side groups" are known in the art at the time of filing (see rejections below); however, only limited numbers of such conjugates were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of conjugates with other types of backbones (i.e. sugar-phosphate backbone of DNA). The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures.

The limitation that the "hapten molecules" and "marker groups or solid phase binding groups" are linked via "reactive side groups" (and specifically the "reactive amino side groups" or "reactive thiol side groups" recited in instant claim 80 and elsewhere), adds to the unpredictability because it is unclear where such groups would be present in a conjugate comprising an oligonucelotide carrier. One of ordinary skill could not guess, *a priori*, how to make and use the claimed conjugates that comprise a polymeric carrier that is made up of monomer units that are nucleotides. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible "reactive side groups" that would link "hapten molecules" and "marker groups or solid phase binding

groups" to a sugar-phosphate backbone. Moreover, although oligonucleotides are known to adopt helical structure (instant claim 85) the specification fails to teach how to make and use such helically structured carriers in the instant invention (i.e. where and to what groups are the "hapten molecules" and "marker groups or solid phase binding groups" attached?). Thus, the instant specification fails to identify that structure which is required for the claimed function.

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have only provided examples of conjugates containing amino acid carriers with luminescent metal chelate marker groups and small organic molecule haptens that are attached through reactive amino side groups. Thus, the teachings of the instant specification coupled with the examples only support conjugates comprising *specific* polymeric carriers that comprise amino acids (or modified versions thereof).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In claims 72, 74-77, 80, 81, 83-88, 100, 101 and 106 there is only the broad recitation that the claimed conjugates comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-

10 "hapten molecules" and 1-10 "marker groups or solid phase binding groups". These moieties are attached to the polymeric carrier via "reactive side groups" at "predetermined positions". However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed conjugates, i.e. when the polymeric carrier comprises nucleotides. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 72, 77, 80, 85, 87, 100, 101, 103, 105 and 106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 72, 77, 100, 101, 103, 105 and 106 recite "solid phase binding group". This is deemed to be indefinite as it is unclear what is the structure of such

groups and the nature of the "solid phase binding" interaction. Is the phrase "solid phase binding" meant to encompass any type of binding – covalent, non-covalent, etc? Are the groups merely functionalities that can bind to any solid phase?

B. Claims 72, 80, 100, 101, 103, 105 and 106 recite "reactive side groups". It is unclear exactly where these groups are located, i.e. what is the "side" of the polymeric carrier? This is especially true when the carrier comprises nucleotide monomers.

C. Claims 72, 103, 105 and 106 recite "non-immunologically reactive". This is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a clear standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, "non-immunologically reactive" under what conditions (in what assay)? A conjugate may be "immunologically reactive" in one assay and "non-immunologically reactive" in another. It is noted that the instant specification discusses the term "non-immunologically reactive" on page 16 (1st paragraph) but this discussion is completely open ended. For example, the specification states that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application".

D. Claim 85 is indefinite because it recites that the "polymeric carrier has a helical structure". This is deemed to be indefinite because it is unclear how

the carriers are to have such a structure. Specifically, is this structure is to be present before or after the addition of the "hapten molecules" and "marker groups or solid phase binding groups"?

E. Claim 87 is indefinite because it recites that the haptens are "pharmacologically active substances". The term "pharmacologically active" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, how "active" must a "substance" be in order to meet the limitations of this claim? What is the structure of such "substances"?

F. Claim 101 recites that the "reactive side groups coupling the hapten molecules and the reactive side groups coupling the marker groups or solid phase binding groups are alike". The term "alike" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, how "alike" must these side groups be in order to meet the limitations of this claim? Same reactivity? Same coupling reaction? Structurally "alike" before reaction? Completely chemically identical? This adds considerable confusion to the claim.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 72, 74-77, 80, 81, 83, 86, 87, 101, 103, 105 and 106 are rejected under 35 U.S.C. 102(b) as being anticipated by Bredehorst et al (Anal. Biochem., 1991; of record).

Bredehorst et al disclose a "novel trifunctional carrier molecule for the synthesis of hapten-fluorophore conjugates" (see Abstract). The carrier of Bredehorst et al consists of the 21 amino acids of the insulin A-chain; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 21 monomeric units. One hapten (2,4-dinitrophenol (DNP)) and three fluorophores (fluorescein) are covalently attached to the carrier; see structure in Figure 1 of the reference. This reads on the limitations of claims 76 and 77 with respect to numbers of entities and claim 81 with respect to fluorescent "marker groups". The hapten is attached to a reactive amino group of the carrier (page 275, 1st column), which reads on the limitations of claim 80.

The carrier of Bredehorst et al also contains four Cys residues that are derivatized to S-sulfonates. As these modified residues are not naturally occurring amino acids, this reads on the "artificial" amino acids of claim 103.

Also, the sulfonates are present in the charged form (to minimize hydrophobicity, see Bredehorst page 275, 1st column and Figure 1), which reads on the carrier containing charged groups (claim 83).

The hapten (DNP) has a molecular weight of about 170, which reads on the limitation of claim 86 and is a "pharmacologically active substance" (claim 87). As it is completely unclear how "alike" the reactive groups must be to be encompassed by the limitations of claim 101, the conjugate of Bredehorst is deemed to read on the conjugates of instant claim 101 as both the hapten and the fluorophore have a nitrogen in the attachment group (amine and azide, respectively).

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Bredehorst et al disclose that their conjugate displays a decrease in non-specific binding (page 278, Table I) and higher sensitivity (page 277, 1st column) than entities without the carrier. Thus for the assay in question (binding to anti-DNP) the carrier clearly is "non-immunologically reactive". Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Bredehorst et al clearly meets this limitation for their intended application.

15. Claims 72, 74, 75, 77, 80, 81, 83, 86, 87, 100, 101, 103, 105 and 106 are rejected under 35 U.S.C. 102(b) as being anticipated by Buchardt et al (WO 92/2073; of record).

Buchardt et al disclose a peptide nucleic acid with a polyamide backbone which has various groups attached to the side chains of the backbone (see Abstract). The compounds of Buchardt et al read on the claimed conjugates as described below.

The "polymeric carrier" in Buchardt et al consists of the polyamide backbone of up to 61 units (see page 7 of the reference); this reads on the limitations of claims 74 and 75 where the monomers are modified amino acids and the carrier has up to 61 monomeric units. Buchardt et al specifically discloses an example of a carrier with 12 units in Figure 5. As the peptide nucleic acids of Buchardt are not naturally occurring amino acids, this reads on the "artificial" amino acids of claim 103.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". Nucleobases are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The conjugate of Figure 5 has 10 nucleobases and also contains an acridine moiety. As acridine is a known fluorophore, this reads on the claimed "marker group". The compounds of Buchardt et al are made on a solid support via coupling at the amine end of the molecule and thus have a "solid phase binding group" of NH_2; see solid phase synthesis of Example 18(b) of the reference. Thus the conjugate of Buchardt in

Figure 5 has 10 "haptens" (nucleobases), 1 fluorescent "marker group" (acridine) and one "solid phase binding group" (NH_2); this reads on the limitations of claim 77 and 100 with respect to numbers of entities and claim 81 with respect to fluorescent "marker groups". The hapten is attached to a reactive amino group of the carrier (amino group of backbone), which reads on the limitations of claim 80.

Buchardt et al also exemplifies a backbone containing a charged residue (see Figure 5), which reads on the carrier containing charged groups (claim 83). As it is completely unclear how "alike" the reactive groups must be to be encompassed by the limitations of claim 101, the conjugate of Buchardt is deemed to read on the conjugates of instant claim 101 as the hapten, the fluorophore and the "solid phase binding group" have a nitrogen in the attachment group.

Lastly, as the conjugates of Buchardt clearly are disclosed to make helical structures (page 9, line 14 though page 10, line 32; pages 87-92 and Examples 56-61, for example), and that conjugates containing acridine (a fluorophore) are used in these experiments (page 91, line 6), claim 85 is anticipated.

16. Claims 72, 74, 75, 80, 86, 87, 88, 100 and 106 are rejected under 35 U.S.C. 102(b) as being anticipated by Tam (US 5,229,490).

Tam discloses a "multiple antigen peptide" system where "a large number of antigens are bound to the functional groups of a dendritic core molecule" (see

Abstract). These "multiple antigen peptide" systems read on the claimed conjugates as described below.

The "polymeric carrier" in Tam consists of a dendritic core molecule, which in Figure 1 is shown as consisting of 8 amino acid residues; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 8 monomeric units. Eight peptide antigens (i.e. hapten) moieties are attached to the dendritic core molecule of Tam. The haptens are attached to reactive amino groups (Lys) of the carrier (see column 5, line 33-53), which reads on the limitations of claim 80.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". The peptide antigens of Tam are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The peptide antigens of Tam specifically read on the exact same "immunogenically reactive peptide epitope" haptens claimed in the instant claim 88. See discussion of peptide antigens found in Tam column 5, line 64 through column 7, line 64, especially the antigens set forth in Table 1).

The conjugates of Tam are made on a solid support via coupling at one end of the molecule (at the –OH moiety of the 1st amino acid of the carrier) and thus have a "solid phase binding group" of -OH; see solid phase synthesis described in Example 2 of the reference. Thus the conjugate of Tam in Figure 1

has 8 "haptens" (peptide antigens) and one "solid phase binding group" (-OH); this reads on the limitations of claim 100 with respect to numbers of entities.

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Tam disclose that their dendritic core molecule (i.e. the carrier) clearly is not antigenic thus is "non-immunologically reactive" (see, for example, column 3, lines 31-48 of the reference). Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Tam clearly meets this limitation for their intended application (see Examples 13 & 14 of the reference).

17. Claims 72, 74, 75, 76, 80, 86, 87, 88, 100 and 106 are rejected under 35 U.S.C. 102(e) as being anticipated by Rose et al (US 6,001,364).

Rose et al disclose compositions of matter comprising "baseplates having a plurality of oxime forming complementary reactive groups" that are attached to "reactive molecules" (see Abstract). The multivalent molecules of Rose et al (see column 7, lines 16-22) read on the claimed conjugates as described below.

The "polymeric carrier" in Rose et al consists of their "baseplate" molecule (see column 7, lines 26-37) which in Figure 1 is shown as consisting of 9 amino acid residues; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 9 monomeric units. Six peptide

antigens (i.e. hapten) moieties are attached to the "baseplate" molecule of Rose et al in Figure 1, reading on the limitations of claim 76. The haptens are attached to reactive amino groups (Lys and amine terminus) of the carrier (see column 3, lines 63-65 and column 10, lines 30-44), which reads on the limitations of claim 80.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". The peptide active molecules of Rose et al (denoted COSMs) are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The COSMs of Rose et al specifically read on the exact same "immunogenically reactive peptide epitope" haptens claimed in the instant claim 88. See discussion of peptide COSMs found in Rose et al column 5, line 60 through column 6, line 17. See also Example II which describes the synthesis and origin of the various peptide COSMs.

The conjugates of Rose et al are made on a solid support via coupling at one end of the molecule (at the –OH moiety of the 1st amino acid of the baseplate) and thus have a "solid phase binding group" of -OH; see solid phase synthesis of the baseplate described in Example I of the reference. Thus the conjugate of Rose et al in Figure 1 has a peptide "baseplate" of sequence GGGKKKKKG; 6 "haptens" (peptide COSMs of sequence KLEEQRPERVKG) and one "solid phase binding group" (-OH); this reads on the limitations of claim 100 with respect to numbers of entities. Moreover, Rose et al teach a conjugate containing

a biotin group which would also read on the claimed "solid phase binding group", see Example VIII in column 22 of the reference. Rose also teaches conjugates attached to a solid surface via thiol chemistry, see Example VIII in column 22-23.

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Rose et al disclose that their "baseplate" (i.e. the carrier) clearly is not antigenic thus is "non-immunologically reactive" (see, for example, column 14, lines 7-26 of the reference). Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Rose et al clearly meets this limitation for their intended applications (see column 15, line 62 through column 16, line 22 and Example VII).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were

made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 72, 74, 75, 80, 81, 86, 87, 88, 100, 103, 104 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tam (US 5,229,490).

The teachings of Tam are set forth supra. The reference lacks the specific exemplification of using "artificial" amino acids, specifically β-alanine, in the polymeric carrier (instant claims 103 & 104). The reference also lacks the specific exemplification of using a labeling group (i.e. the instant "marker groups" of claim 81).

However, the reference sets forth in column 5, lines 27-32 that the use of additional residues in extending the dendritic core molecule ("polymeric carrier") for peptide antigens of short chain length (6-14 residues) is preferred. The reference specifically sets forth β-alanine for such a purpose (column 5, line 30).

Also, Tam teaches that in using their conjugates for testing that "the diagnostic moiety joined to the dendritic polymer may be labeled with a detectable label" (column 10, lines 44-55). The reference sets forth fluorescent labels as a "useful" type of such groups (column 10, lines 48-50).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use β-alanine as a part of the dendritic core molecule ("polymeric carrier") of Tam and/or use a detectable fluorescent label as the reference describes these modifications specifically. One of ordinary skill would have been motivated to use β-alanine in the carrier when the peptide antigen of interest is of short chain length (6-14 residues) as set forth by Tam. One of ordinary skill would have been motivated to use a detectable fluorescent label when necessary for the test of interest as set forth by Tam (see column 10, lines 40-55). One of ordinary skill would also have had a reasonable expectation of success based on the fact that the synthesis of the polymeric carriers of Tam are carried out using standard techniques thus were well known and routine in the art at the time of filing (see Example 1 of the reference). Methods of labeling are also well known, as taught by Tam (column 10, lines 54-55).

21. Claims 72, 73, 74, 75, 76, 80, 81, 86, 87, 88, 100, 103 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rose et al (US 6,001,364).

The teachings of Rose et al are set forth supra. The reference lacks the specific exemplification of using "artificial" amino acids in the polymeric carrier (instant claims 103). The reference also lacks the specific exemplification of using a labeling group, specifically metal chelates (i.e. the instant "marker groups" of claim 73 & 81).

However, the reference sets forth in column 7, line 23 through column 8, line 2 that the use of "artificial" amino acid residues in the baseplate molecule

(i.e. "polymeric carrier") is preferred. The reference specifically sets forth using β-amino acids for such a purpose (column 7, line 37-41 & column 7, line 66 through column 8, line 2).

Also, Rose et al teaches that in their conjugates can comprise metal chelates as they are also considered to be haptens (see column 6, lines 13-17; column 12, line 62 through column 13, line 13 & column 14, lines 12-26) and/or can be a part of the complementarity determining region of an antibody (see column 14, lines 39-46). The reference also teach polyoxime conjugates containing "signal producing groups" (see Example VIII in column 22) and the use of "reporter groups" (column 13, lines 46-64) all reading in the instant "marker groups".

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use β-amino acids as a part of the basplate ("polymeric carrier") of Rose et al and/or use a detectable signal or reporter groups that are metal chelates as the reference describes these modifications specifically. One of ordinary skill would have been motivated to use β-amino acids in the carrier as these are preferred residues as set forth by Rose (column 7, line 66 through column 8, line 2). One of ordinary skill would have been motivated to use a detectable signal or reporter groups that are metal chelates when necessary for the test of interest as set forth by Rose (see column 13, lines 53-65 & column 14, lines 42-46). One of ordinary skill would also have had a reasonable expectation of success based on the fact that the synthesis of the

polymeric carriers of Rose are carried out using standard techniques thus were well known and routine in the art at the time of filing (see Example 1 of the reference). Methods of labeling are also well known, as taught by Rose (column 14, lines 21-23 & 42-50).

22. Claims 72-77, 80, 81, 83, 84, 86, 87, 101, 103, 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst et al (Anal. Biochem., 1991; of record) in view of Bard (US 5,310,687; of record).

The teachings of Bredehorst et al are set forth supra. The reference lacks the specific use of a luminescent metal chelate as the "marker group" (claims 73 and 84).

However, the use of luminescent metal chelates as marker or labeling groups in conjugates was well known in the art at the time of filing. For example, Bard et al teach electrochemiluminescent organometallic compounds that are used as labels for detecting low concentrations of chemical moieties (see Abstract). Bard et al describe using their luminescent metal chelates in a variety of systems (see column 1, lines 13-33) and specifically set forth that the metal chelates are covalently attached to a biological substance (see patented claim 1 and column 9, lines 7-40). Specific chelates are described by Bard in columns 10-11 of the reference. Bard et al teach that suitable conditions for creating the conjugates are known in the art (column 13, lines 34-43, for example) and also specifically teach

attaching their luminescent metal chelates to BSA and antibodies (see Examples III, IV and V of the reference).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the luminescent metal chelates of Bard in place of the fluorophore of Bredehorst as both the metal chelate and the Bredehorst are known in the art to be marker or labeling groups. One of ordinary skill would have been motivated to do so as the metal chelates of Bard allow for detection at low concentrations (see Abstract) and provide measurements that are "sensitive, fast, reproducible and utilize simple instrumentation" (see column 12, lines 50-68). Furthermore, Bard et al specifically teach that their luminescent metal chelates are superior to a fluorphore in a comparison study (See Example VII of the reference).

Status of Claims/Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie E. Garcia, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday from 8:30 to 6:00 and alternate Fridays.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie E. Garcia, Ph.D.
January 8, 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER

Application No.: 08/776,190

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:_____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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